#12
C.D.

PATENTS 3/19/02

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

David N. COOPER et al.

Serial No. 09/853,688 GROUP 1623

Filed May 14, 2001 Examiner Unassigned

METHOD FOR DETECTING GROWTH HORMONE VARIATIONS IN HUMANS, THE VARIATIONS AND THEIR USES

INFORMATION DISCLOSURE STATEMENT

Commissioner for Patents

Washington, D.C. 20231

Sir:

In compliance with Rules 1.97 and 1.98, and in fulfillment of the duty of disclosure under Rule 1.56, the accompanying documents, copies of which are attached to this statement, are made of record on the enclosed sheet.

A concise explanation of the relevance of these items is that these references were cited in the International Search Report in the corresponding International application Serial No. PCT/GB01/02126. A copy of the International Search Report in which they were cited is attached hereto.

Respectfully submitted,

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March 12, 2002'

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PATENT COOPERATION TREATY

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PCT

From the INTERNATIONAL SEARCHING AUTHORITY

To:
WYNNE-JONES LAINE & JAMES
Morgan Arcade Chambers
Attn. Newell, William Joseph
33 St. Mary Street
Cardiff CF10 1AF
UNITED KINGDOM

INVITATION TO PAY ADDITIONAL FEES

(PCT Article 17(3)(a) and Rule 40.1)

Diary 31.12.01
7.1.02
Pay fees by 10.1.0

Applicant's or agent's file reference WN/WCM.78	Date of mailing *(day/month/year)* 10/12/2001
International application No. PCT/GB 01/02126	**PAYMENT DUE** within 30 ~~months~~/days from the above date of mailing
Applicant UNIVERSITY OF WALES COLLEGE OF MEDICINE et al.	International filing date *(day/month/year)* 14/05/2001

1. This International Searching Authority

(i) considers that there are 44 *(number of)* inventions claimed in the international application covered by the claims indicated ~~below~~/on the extra sheet:

and it considers that the international application does not comply with the requirements of unity of invention (Rules 13.1, 13.2 and 13.3) for the reasons indicated ~~below~~/on the extra sheet:

(ii) [X] has carried out a partial international search (see Annex) [ ] will establish the international search report on those parts of the international application which relate to the invention first mentioned in claims Nos.:
see extra sheet first invention

(iii) will establish the international search report on the other parts of the international application only if, and to the extent to which, additional fees are paid

2. The applicant is hereby **invited,** within the time limit indicated above, to pay the amount indicated below:

GBP 624,00 (Fee per additional invention) x 43 (number of additional inventions) = GBP 26.832,00 (total amount of additional fees)

Or, EUR 945,00 x 43 = EUR 40.635,00

The applicant is informed that, according to Rule 40.2(c), **the payment of any additional fee may be made under protest,** i.e., a reasoned statement to the effect that the international application complies with the requirement of unity of invention or that the amount of the required additional fee is excessive.

3. [X] Claim(s) Nos. further info. have been found to be unsearchable under Article 17(2)(b) because of defects under Article 17(2)(a) and therefore have not been included with any invention.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Catherine Humbert

Form PCT/ISA/206 (July 1992)

Annex to Form PCT/ISA/206
COMMUNICATION RELATING TO THE RESULTS OF THE PARTIAL INTERNATIONAL SEARCH

International Application No
PCT/GB 01/02126

1. The present communication is an Annex to the invitation to pay additional fees (Form PCT/ISA/206). It shows the results of the international search established on the parts of the international application which relate to the invention first mentioned in claims Nos.:
see 'Invitation to pay additional fees'
2. This communication is not the international search report which will be established according to Article 18 and Rule 43.

3. If the applicant does not pay any additional search fees, the information appearing in this communication will be considered as the result of the international search and will be included as such in the international search report.

4. If the applicant pays additional fees, the international search report will contain both the information appearing in this communication and the results of the international search on other parts of the international application for which such fees will have been paid.

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PROCTER ANNIE M ET AL: "The molecular genetics of growth hormone deficiency." HUMAN GENETICS, vol. 103, no. 3, 1998, pages 255-272, XP000990238 ISSN: 0340-6717 page 258, right-hand column page 259, right-hand column -page 260 page 262, left-hand column, paragraph 3 page 262, right-hand column, paragraphs 4,5 page 264, right-hand column -page 267 ---	1-11, 23-28, 34-36,38
X	HASEGAWA YUKIHIRO ET AL: "Identification of novel human GH-1 gene polymorphisms that are associated with growth hormone secretion and height." JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 85, no. 3, March 2000 (2000-03), pages 1290-1295, XP000990096 ISSN: 0021-972X cited in the application the whole document --- -/--	1-11, 23-28, 34-36,38

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MIYATA ICHIRO ET AL: "Detection of growth hormone gene defects by dideoxy fingerprinting (ddF)." ENDOCRINE JOURNAL, vol. 44, no. 1, February 1997 (1997-02), pages 149-154, XP000990097 ISSN: 0918-8959 cited in the application the whole document	1-11, 23-28, 34-36,38
X	CHEN E Y ET AL: "THE HUMAN GROWTH HORMONE LOCUS NUCLEOTIDE SEQUENCE BIOLOGY AND EVOLUTION" GENOMICS, vol. 4, no. 4, 1989, pages 479-497, XP000990095 ISSN: 0888-7543 cited in the application the whole document	28, 34-36,38
X	EP 0 790 305 A (JAPAN CHEM RES) 20 August 1997 (1997-08-20) page 5, line 49 -page 6, line 9	28,30, 34-36,38
X	US 5 849 535 A (OLSON KENNETH ET AL) 15 December 1998 (1998-12-15) example 2	28,30, 34-36,38
A	O'DONOVAN MICHAEL C ET AL: "Blind analysis of denaturing high-performance liquid chromatography as a tool for mutation detection." GENOMICS, vol. 52, no. 1, 15 August 1998 (1998-08-15), pages 44-49, XP002163295 ISSN: 0888-7543 cited in the application the whole document	9
A	ROSENFELD, R. G.: "Editorial: Is growth hormone deficiency a viable diagnosis?" JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, vol. 52, no. 2, 1997, pages 349-351, XP000990384 page 349	1-11, 13-44
A	WO 93 00445 A (UNIV VANDERBILT) 7 January 1993 (1993-01-07) example 1	1-11, 13-44

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International Application No
PCT/GB 01/02126

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WAGNER JOHANN K ET AL: "Allelic variations in the human growth hormone-1 gene promoter of growth hormone-deficient patients and normal controls." EUROPEAN JOURNAL OF ENDOCRINOLOGY, vol. 137, no. 5, November 1997 (1997-11), pages 474-481, XP000990216 ISSN: 0804-4643 the whole document	1-11, 13-44

INVITATION TO PAY ADDITIONAL FEES

International application No.
PCT/GB 01/02126

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-11,23-27 all completely ; 13-19,21,22, 28-44 all partially

invention 1:

Detection methods for a variation in GH1, a screening method for determining GH dysfunction, the GH1 variant having the mutation Arg64Gly (AGG to GGG):799, a screening method analysing the sequence of this variant, a kit for the detection of this variant, a composition comprising this variant, a nucleic acid encoding this variant or hybridising to this variant, a vector containing this nucleic acid, a host cell comprising this vector, a protein encoded by this nucleic acid and a process for producing this variant, and the use of this variant.

2. Claims: 13-19,21,22,28-44 all partially

invention 2:

The GH1 variant having the mutation Leu163Pro (CTC to CCC):1442, a screening method analysing the sequence of this variant, a kit for the detection of this variant, a composition comprising this variant, a nucleic acid encoding this variant or hybridising to this variant, a vector containing this nucleic acid, a host cell comprising this vector, a protein encoded by this nucleic acid and a process for producing this variant, and the use of this variant.

inventions 3-21:

idem for every single GH1 variant characterised as unpublished in table 7B ("mutation") of the application.

3. Claims: 16,17,21,22,28-44 all partially

invention 22:

The GH1 variant having the mutation T to C at -495, a screening method analysing the sequence of this variant, a kit for the detection of this variant, a composition comprising this variant, a nucleic acid encoding this variant or hybridising to this variant, a vector containing this nucleic acid, a host cell comprising this vector, a protein encoded by this nucleic acid and a process for

producing this variant, and the use of this variant.

inventions 23-27:

idem for every single GH1 variant claimed in claim 16 that was not characterised as unpublished in table 7B ("mutation") of the application..

4. Claims: 18-20,32-44 all partially

invention 28:

The GH1 variant having the amino acid substitution Met to Val -26, a screening method analysing the sequence of this variant, a composition comprising this variant, a nucleic acid encoding this variant or hybridising to this variant, a vector containing this nucleic acid, a host cell comprising this vector, a protein encoded by this nucleic acid and a process for producing this variant, and the use of this variant.

inventions 29-44:

idem for every single GH1 variant claimed in claim 18 that was not characterised as unpublished in table 7B ("mutation") of the application.

The problem to be solved by the current application is to provide growth hormone 1 (GH1) variants with the help of new detection methods. The variants can then be used as indicators of GH dysfunctions.
GH variants, products related to them and methods using them are well known in the state of the art.
HASEGAWA YUKIHIRO ET AL: "Identification of novel human GH-1 gene polymorphisms that are associated with growth hormone secretion and height." JOURNAL OF CLINICAL ENDOCRINOLOGY & METABOLISM, vol. 85, no. 3, March 2000 (2000-03), pages 1290-1295, XP000990096 ISSN: 0021-972X (D1) discloses promoter and intron polymorphisms in GH1, and the link of polymorphisms to low hormone level and height. The polymorphism 1663 discloses in D1 is polymorphism 1169 of the current application.
MIYATA ICHIRO ET AL: "Detection of growth hormone gene defects by dideoxy fingerprinting (ddF)." ENDOCRINE JOURNAL, vol. 44, no. 1, February 1997 (1997-02), pages 149-154, XP000990097 ISSN: 0918-8959 (D2) discloses the PCR amplification, and RFLP analysis of GH1. The GH1 mutation in exon 1, that is disclosed in D2 causes the Thr24Ala substitution that has been detected with the method of the current application as well.

Each of the two documents disclose variants of GH1 (mutations/polymorphisms) that are linked to GH dysfunctions.
In the light of any of the 2 documents D1 and D2 the problem to be solved by the current application is to provide further GH variants and products and methods based on them.
Thus every single variant together with the products and methods related to the single variant, has to be regarded as a single invention on its own.
Due to the essential differences in the primary structures of the variants ,and due to the fact that no other technical features can be distinguished which in the light of the state of the art could be regarded as special technical features common to the solutions to the problem denoted above, the ISA is of the opinion, that there is no single inventive concept underlying the inventions of the current application in the sense of rule 13.1 PCT.
Consequently there is a lack of unity, and the different solutions given, each representing a different invention not belonging to a common inventive concept are formulated as different subjects on the communication pursuant to Art. 17 (3) (a) PCT.
The ISA has searched the first invention listed above (claims 1-11,23-27 all completely ; 13-19,21,22,28-44 all partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 206

Continuation of Box 3.

Claims Nos.: 12

Present claim 12 relates to products defined by reference to a desirable characteristic or property, namely to variants that are characterised by being detected or detectable by some of the methods claimed in the application, but not having been detected by other methods.
In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 84 EPC). Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, no search has been carried out for this claim.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Patent Family Annex

Information on patent family members

International Application No
PCT/GB 01/02126

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0790305 A	20-08-1997	AU 723494 B2	31-08-2000
		AU 1266497 A	21-08-1997
		BR 9700957 A	08-12-1998
		CA 2197408 A1	14-08-1997
		EP 0790305 A1	20-08-1997
		US 6238915 B1	29-05-2001
		JP 10080277 A	31-03-1998
US 5849535 A	15-12-1998	US 6057292 A	02-05-2000
		US 6004931 A	21-12-1999
		US 6136563 A	24-10-2000
		AU 718439 B2	13-04-2000
		AU 7073396 A	09-04-1997
		EP 0851925 A1	08-07-1998
		JP 11512298 T	26-10-1999
		WO 9711178 A1	27-03-1997
		ZA 9607973 A	23-06-1997
WO 9300445 A	07-01-1993	WO 9300445 A1	07-01-1993